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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/632,725
Filing Date: August 01, 2003
Appellant(s): WOLF ET AL.

Allison Johnson
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 9/26/2007 appealing from the Office action mailed 4/26/2007.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

The amendment after final rejection filed on 8/24/2007 has been entered.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are as follows:

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner. Whether claims 59-66 and 118-138 should be rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

The amendment after final rejection filed on 8/24/2007 has been entered.

(8) Evidence Relied Upon

6,582,903	RIGLER	07-19995
6,515,289	KASK	12-1999
20030138853	LAHIRI	08-2000

Dorland's Illustrated Medical Dictionary, Twenty-fifth Edition, Saunders, Philadelphia (1979), p. 1148.

Robbins and Cotran, Pathologic Basis of Disease, Second Edition, W.B. Saunders Co., Philadelphia, (1979), at pp. 22-26.

Rigler, Fluorescence correlation, single molecule detection and large number screening, Applications in biotechnology, Journal of Biotechnology, vol. 41 (1995), pp. 177-186.

Weiner et al., Rapid and Reproducible Quantification of Hepatitis C Virus cDNA by Fluorescence Correlation Spectroscopy, Digestion, 2000, vol. 61, pp. 84-89.

Walter et al., Fluorescence correlation analysis of probe diffusion simplifies quantitative pathogen detection by PCR, Proc. Natl. Acad. Sci. USA, November 1996, vol. 93, pp. 12805-12810.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

(9) Claim Rejections - 35 USC § 112, First Paragraph

1. Claims 132-137 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is for new matter.

This rejection is necessitated by appellant's amendments to the claims.

Claims 132-137 state limitations drawn to analyzing occurring over particular ranges of seconds. These limitations do not appear to find support in the specification as filed. Appellant must point with particularity as to where these limitations are to be found in the specification as filed.

Appellant's Arguments After Final Rejection

Appellant points the drawings for providing support for the limitation of "over a period of second". The examiner respectfully submits that this is not

persuasive, because the drawings do not provide support for an open-ended duration of seconds, as claimed.

(9) Claim Rejections - 35 USC § 112, Second Paragraph

2. Claims 59, 118-121, 124-126, 130-132, 134 and 136 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which appellant regards as the invention.

This rejection is reiterated for the reasons of record as set forth in the previous Office action. This rejection is necessitated by appellant's amendments to the claims.

Claim 59 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: determining the presence or absence of the pathogen.

Response to Arguments after Final Rejection

Appellant argues that the claims include all required elements or steps.

Appellant's arguments, entered 6/26/2007, have been fully considered but they are not persuasive. Claim 59 is vague and indefinite because it is unclear that the method steps are for the method as set forth in the preamble. The preamble is drawn to assaying for a pathogen. The instant rejection could be

overcome by a final step drawn to "thereby assaying for a pathogen in the sample".

3. Claims 131-133 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which appellant regards as the invention.

Appellant's usage of the language of "identity of said pathogen is unknown" appears to read upon a mental step. It unclear as to who or what the identity of the pathogen is "unknown" or the distinguishing physical feature of a pathogen that is unknown. It is unclear as to whether the language refers to a mental step or attempts to refer to a structural limitation of the claimed product. It is not disputed that appellant may be their own lexicographer. The examiner does not argue that the term is repugnant to the usual usage in the art. Rather, it is that claim 131 does not reasonably apprise of one skill in the art as to the metes and bounds of the claimed invention.

Claims 132 and 133 recite the limitation wherein the analyzing occurs over a period of seconds, which renders the claims vague and indefinite, because the limitation is tantamount to claiming that the analyzing occurs over a period of time, and so would not apprise one of skill in the art of the metes and bounds of the claimed invention.

Response to Arguments after Final Rejection

Appellant argues that identity of a pathogen might be unknown at the time of sampling.

Appellant's arguments, entered 6/26/2007, have been fully considered but they are not persuasive. The pathogen unknown at the time of sampling may be a species previously known to science. The quality of being known or unknown, is thus dependent upon the practitioner of the method; but does not affect the pathogen, itself. As such, one of skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention.

(9) Claim Rejections - 35 USC § 102

4. Claims 59-66 and 118-125, 127, 128, 130-133, and 138 are rejected under 35 U.S.C. 102(e) as being anticipated by Rigler et al., US 6,582,903 B1.

This rejection is maintained for the reasons of record as set forth in the previous Office action. That rejection is copied below for the convenience of the reader. This rejection is necessitated by appellant's amendments to the claims.

The claims are drawn to methods of assaying for a pathogen in a sample, said method comprising: exciting said sample with radiation, said sample comprising at least one pathogen; at least one probe, and at least one fluorescent tag; measuring the fluorescence from a subvolume of said excited sample; and analyzing the fluctuations of said fluorescence that are due to the diffusion or flow of said pathogen through said subvolume; and variations thereof.

Rigler et al., throughout the patent, and at col. 16, line 47, teach detecting pathogens reading on method of assaying for the presence of a pathogen component in a sample; Rigler et al., e.g., at col. 1, lines 55-58, teach

fluorescence correlation spectroscopy (FCS) using chromophorous molecular structures having fluorescence properties, reading on fluorophores; wherein the fluorophorous molecules in solution are exposed to the intense exciting light of a laser, (Rigler et al. at col. 2, lines 21-24), which reads on exciting a sample with radiation, said sample comprising a complex of a target molecule to be detected and a labeled test reagent, (Rigler et al., at col. 7, lines 14-27), the receptor molecules/ligands, (Rigler et al., col. 8, lines 50-64), including antibodies, which reads further on at least one probe capable of binding a predetermined pathogen component, and at least one fluorescent tag, (Rigler et al., col. 13, lines 45-62; col. 18, line 41-col. 19, line 2); measuring fluorescence from a volume element, reading on measuring the fluorescence from a subvolume of said sample, (see col. 12, line 62-col. 13, line 10; col. 13, line 62-col. 14, line 45); analyzing the fluctuations of said fluorescence, (Rigler et al., at col. 2, line 7-20); and determining the presence or absence of said pathogen component, (Rigler at col. 8, lines 25-30; col. 16, lines 36-47).

Rigler et al. at col. 2, line 7-31, teach that spectroscopic methods for measuring fluorescence fluctuations are employed in fluorescence correlation spectroscopy. In considering the disclosure of the instant application in regards to measuring fluctuations in fluorescence intensity in fluorescence correlation spectroscopy, the examiner respectfully notes that the instant specification states:

> Fluorescence correlation spectroscopy (FCS) is a single molecule detection method that measures the fluctuations in fluorescence intensity in a small (e.g., femtoliter) confocal volume. FCS employs

> a tightly focused laser beam to define the confocal volume. The diffusion of fluorescently labeled particles into and out of the illuminated volume determines the fluorescence intensity fluctuation patterns. From this data, one can extract both qualitative information and quantitative information on the molecule being studied. Such qualitative information includes, e.g., the presence or absence of molecular interaction; such quantitative information includes diffusion time, stoichiometry of the interactions, concentration of the interacting particles and the kinetics of the interaction.

Specification at pp. 1-2, bridging paragraph.

Rigler et al., at col. 12, lines-22, teach at least two differently labeled test reagents which will bind to different sequence segments of an analyte, and teach cross correlation of a chromophore 1 and a chromophore 2, (col. 13, line 45-col. 14, line 9), reading on a plurality of unique fluorescently tagged probes, as in claims 62 and 63. Rigler at col. 11, line 45-col. 12, line 22, teaches determining the crosscorrelation function and the autocorrelation function of a sample, reading on claim 64. Rigler at col. 25, lines 10-25, col. 35, lines 57-65, teach pathogens that comprise bacteria or virus, as in claims 65 and 66.

Response to Arguments, Mailed 4/26/2007

Appellant argues Rigler does not disclose a method for assaying a pathogen in a sample, in a sample volume that includes one pathogen. Appellant's representative states: "A molecule is not a pathogen. A pathogen is an organism. In addition a pathogen is an agent that causes a disease state", (Reply at p. 25).

Appellant's arguments, entered 10/23/2006, have been fully considered but they are not persuasive.

Firstly, as stated in the previous Office action, claims must be given their broadest reasonable interpretation consistent with the supporting description. In re Hyatt, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). The claims are drawn to pathogens. See, *e.g.*, *Invitrogen Corp v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 1997); and MPEP 211.03. The claims and the specification do not provide a limiting definition for the term "pathogen". Dorlands's Illustrated Medical Dictionary, Twenty-fifth Edition, Saunders, Philadelphia (1979) at p. 1148, defines the term pathogen as "any disease-producing microorganism **or material**." Emphasis added. Therefore, the examiner respectfully submits that the term pathogen, when given its broadest reasonable interpretation, is taught by reference of Rigler.

The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a *prima facie* case of obviousness."). MPEP 2145. Appellant's representative states: "A molecule is not a pathogen. A pathogen is an organism. In addition a pathogen is an agent that causes a disease state", (Reply at p. 25). The examiner respectfully submits that this is merely argument that is insufficient as objective evidence.

Response to Arguments after Final Rejection

Appellant's arguments, entered 6/26/2007, have been fully considered but they are not persuasive. Appellant argues that a pathogen is an organism and

therefore Rigler cannot teach pathogens. Rigler at col. 6, lines 46-60, disclose assaying diffusion times of viruses and cells, including bacteria. The examiner respectfully submits that the term pathogen encompasses more than an organism. Furthermore, the claims are drawn to assaying for a pathogen. Such identification is possible from components of a pathogen.

Appellant argues that Rigler does not teach analysis of diffusion or flow of a pathogen through a subvolume. The examiner respectfully submits that Rigler teaches fluorescence correlation spectroscopy (FCS) comprising measuring fluorescence from a volume element, reading on measuring the fluorescence from a subvolume of said sample, (see col. 12, line 62-col. 13, line 10; col. 13, line 62-col. 14, line 45); analyzing the fluctuations of said fluorescence, (Rigler et al., at col. 2, line 7-20); and determining the presence or absence of said pathogen component, (Rigler at col. 8, lines 25-30; col. 16, lines 36-47). Rigler, at e.g., col. 2, lines 7-20, teach FCS fluctuation analysis. Rigler at col. 2, lines 21-54, teach the use of fluorophorous molecules. Rigler teaches fluorophorous molecules, including labeled reagents such as antibodies or receptor molecules (col. 8, lines 50-64).

Rigler at col. 25, lines 10-25, col. 35, lines 57-65, teach pathogens that comprise bacteria or virus. See also, Rigler at col. 21, line 62-col 22, line 11. Rigler, e.g., at col. 11, lines 33-45, teach parallel determination of at least two different analytes in a sample, reading on a plurality of probes. The examiner respectfully submits that the term "period of seconds" encompasses time periods of less than one second.

5. Claims 59-64, 66 and 118-125, 127, 128, 130-133, and 138 are rejected under 35 U.S.C. 102(b) as being anticipated by Rigler, Journal of Biotechnology, vol. 41 (1995), pp. 177-186.

This rejection is maintained for the reasons of record as set forth in the previous Office action. That rejection is copied below for the convenience of the reader. This rejection is necessitated by appellant's amendments to the claims.

Rigler (1995), throughout the publication and abstract, and at pp. 182-184, teach methods of assaying for the presence of a pathogen component in a sample, said method comprising: exciting a sample with laser radiation, (Rigler (1995) at p. 178, Fig. 1), said sample comprising at least one probe (Rigler (1995) at p. 178, para 2) capable of binding a predetermined pathogen component, such as hepatitis B and C or HIV and virus that is M13 bacteriophage, (Rigler (1995) at pp. 182-193, bridging paragraph, and as in claim 65) using several fluorescence labeled primers in the form of a cocktail, (also reading on claim 62), reading on methods comprising at least one fluorescent tag, and measuring the fluorescence fluctuations from an extremely small volume element, Rigler (1995), at p. 177, para 1-2), which reads on a subvolume of said sample and analyzing the fluctuations of said fluorescence, and determining the presence or absence of said pathogen component, (Rigler (1995) at pp. 182-193, bridging paragraph).

Rigler (1995), at p. 182, Fig. 6, teaches cross-correlation in two colors, reading on a plurality of probes with different fluorophore tags, and e.g., at p. 180, teach autocorrelations, as in claims 62-64.

Response to Arguments, Mailed 4/26/2007

Appellant argues Rigler does not disclose a method for assaying a pathogen in a sample, in a sample volume that includes one pathogen. Appellant's representative states: "A molecule is not a pathogen. A pathogen is an organism. In addition a pathogen is an agent that causes a disease state", (Reply at pp. 25, 29).

Appellant's arguments, entered 10/23/2006, have been fully considered but they are not persuasive.

Firstly, claims must be given their broadest reasonable interpretation consistent with the supporting description. In re Hyatt, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). The claims are drawn to pathogens. See, *e.g.*, *Invitrogen Corp v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 1997); and MPEP 211.03. The claims and the specification do not provide a limiting definition for the term "pathogen". Dorlands's Illustrated Medical Dictionary, Twenty-fifth Edition, Saunders, Philadelphia (1979) at p. 1148, defines the term pathogen as "any disease-producing microorganism **or material**." Emphasis added. Therefore, the examiner respectfully submits that the term pathogen, when given its broadest reasonable interpretation, is taught by reference of Rigler.

The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a *prima facie* case of obviousness."). MPEP 2145. Appellant's representative states: "A molecule is not a pathogen. A pathogen is an organism. In addition a pathogen is an agent that causes a disease state", (Reply at p. 25). The examiner respectfully submits that this is merely argument that is insufficient as objective evidence.

Response to Arguments after Final Rejection

Appellant's arguments, entered 6/26/2007, have been fully considered but they are not persuasive. Appellant argues that a pathogen is an organism and therefore Rigler (1995) cannot teach pathogens. The examiner respectfully submits that the term pathogen encompasses more than an organism; and that molecules may be considered pathogens. Furthermore, the claims are drawn to assaying for a pathogen. Such identification is possible from components of a pathogen.

Rigler (1995), at p. 178, para 3, teach fluctuation analysis in FCS. Rigler (1995), at p. 182, column 2, discloses assaying diffusion times of viruses, (p. 182).

Appellant argues that Rigler (1995) teaches away from a period of seconds. First, Rigler (1995) anticipates the claimed invention, so that an argument of teaching away is not apropos. Second, Rigler (1995), at e.g., the

abstract, teaches a period of milliseconds. The examiner respectfully submits that the claimed term "period of seconds" encompasses time periods of less than one second.

Rigler (1995), at p. 182, right column, teaches use of several fluorescence labeled primers in the form of a "cocktail", thereby teaching a plurality of probes.

Appellant's arguments regarding claim 65 are persuasive, and the instant rejection of claim 65 over Rigler (1995) is withdrawn.

6. Claims 59-64, 66 and 118-125, 127, 128, 130-138 are rejected under 35 U.S.C. 102(b) as being anticipated by Weiner et al., Digestion, 2000, vol. 61, pp. 84-89.

Weiner et al., throughout the publication, abstract, and at para 1, teach measuring serum hepatitis C virus (HCV) RNA, and teach a fluorescence correlation spectroscopy method (p. 85, Methods, para 7) for assaying the pathogen, HCV in a sample, reading on assaying for the presence of a pathogen component in a sample, said method comprising: exciting a sample with argon-ion laser, radiation, said sample comprising Cy3-labeled amplimers for HCV RNA, (Weiner et al., at p. 85, para 8), reading on a at least one probe capable of binding a predetermined pathogen component, and at least one fluorescent tag; measuring the fluorescence from a subvolume of said sample and measuring diffusion times, (p. 85, para 8), reading on analyzing the fluctuations of said fluorescence; and determining the presence or absence of said HCV.

Response to Arguments, Mailed 4/26/2007

Appellant argues Wiener does not disclose a method for assaying a pathogen in a sample, in a sample volume that includes one pathogen. Appellant's representative states: "The RNA of hepatitis C virus is not a pathogen. Therefore Weiner et al. do not teach a sample that includes a pathogen", (Reply at p 29).

Appellant's arguments, entered 10/23/2006, have been fully considered but they are not persuasive.

Firstly, claims must be given their broadest reasonable interpretation consistent with the supporting description. In re Hyatt, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). The claims are drawn to pathogens. See, *e.g.*, *Invitrogen Corp v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 1997); and MPEP 211.03. The claims and the specification do not provide a limiting definition for the term "pathogen". Dorlands's Illustrated Medical Dictionary, Twenty-fifth Edition, Saunders, Philadelphia (1979) at p. 1148, defines the term pathogen as "any disease-producing microorganism **or material**." Emphasis added. Therefore, the examiner respectfully submits that the term pathogen, when given its broadest reasonable interpretation, is taught by reference of Weiner et al.

The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the

kind of factual evidence that is required to rebut a *prima facie* case of obviousness."). MPEP 2145. Appellant's representative states: "The RNA of hepatitis C virus is not a pathogen", (Reply at p. 29). The examiner respectfully submits that this is merely argument that is insufficient as objective evidence.

Response to Arguments after Final Rejection

Appellant's arguments, entered 6/26/2007, have been fully considered but they are not persuasive. Appellant argues that a pathogen is an organism and therefore Weiner cannot teach pathogens. The examiner respectfully submits that the term pathogen encompasses more than an organism; and that molecules may be considered pathogens. Weiner et al., throughout the publication, abstract, and at para 1, teach measuring serum hepatitis C virus (HCV) RNA, and teach a fluorescence correlation spectroscopy method (p. 85, Methods, para 7) for assaying the pathogen that is the virus hepatitis C. FCS methods inherently employ fluctuation analysis, as stated in the instant specification in the Summary of the Invention. Furthermore, the claims are drawn to assaying for a pathogen. Such identification is possible from components of a pathogen.

Appellant argues that Weiner does not teach analysis of diffusion or flow of a pathogen through a subvolume. The examiner respectfully submits that Weiner teaches fluorescence correlation spectroscopy (FCS) comprising measuring fluorescence from a volume element, reading on measuring the fluorescence from a subvolume of said sample, (see p. 85, second paragraph and last paragraph).

Weiner et al., at p. 85, last paragraph, teach analysis for 60 seconds. The examiner respectfully notes that the claims are rejected under 35 102(b) over Weiner. Weiner, at p. 88, para 6, teach the use of internal control RNAs labeled with different fluorochromes to be processed in the FCS assay for pathogen, thereby reading on a plurality of unique fluorescently tagged probes.

Appellant's arguments regarding claim 65 are persuasive, and the instant rejection of claim 65 over Weiner is withdrawn.

7. Claims 59-65 and 118-125, 127, 128, 130-138 are rejected under 35 U.S.C. 102(b) as being anticipated by Walter et al., Proc. Natl. Acad. Sci., USA, November 1996, vol. 93, pp. 12805-12810.

Walter et al., throughout the publication and abstract and at p.12805, para 1-2, teach a method of assaying for the presence of a *Mycobacterium tuberculosis* pathogen component in a sample, said method comprising: exciting a sample with laser radiation, 9P. 12805, para 1), said sample comprising at least one primer (see Table 1, p. 12807) capable of binding a *M. tuberculosis* DNA pathogen component, and at least one fluorescent rhodamine tag; measuring the fluorescence from a investigated volume (Walter et al. at p. 12805, para 1), reading on a subvolume of said sample; analyzing the fluctuations of said fluorescence, (Walter et al. at p. 12805, para 1); and determining the presence or absence of said pathogen component.

Response to Arguments, Mailed 4/26/2007

Appellant argues Walter et al., does not disclose a method for assaying a pathogen in a sample, in a sample volume that includes one pathogen. Appellant's representative states: "A DNA is not a pathogen. Walter et al. thus fail to teach the method of claim 60", (Reply at p 31).

Appellant's arguments, entered 10/23/2006, have been fully considered but they are not persuasive.

Firstly, claims must be given their broadest reasonable interpretation consistent with the supporting description. In re Hyatt, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). The claims are drawn to pathogens. See, *e.g.*, *Invitrogen Corp v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 1997); and MPEP 211.03. The claims and the specification do not provide a limiting definition for the term "pathogen". Dorlands's Illustrated Medical Dictionary, Twenty-fifth Edition, Saunders, Philadelphia (1979) at p. 1148, defines the term pathogen as "any disease-producing microorganism **or material**." Emphasis added. Therefore, the examiner respectfully submits that the term pathogen, when given its broadest reasonable interpretation, is taught by reference of Walter et al.

The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a *prima facie* case of

obviousness."). MPEP 2145. Appellant's representative states: "A DNA is not a pathogen", (Reply at p. 29). The examiner respectfully submits that this is merely argument that is insufficient as objective evidence.

Response to Arguments after Final Rejection

Appellant's arguments, entered 6/26/2007, have been fully considered but they are not persuasive. Appellant argues that a pathogen is an organism and therefore Walter cannot teach pathogens. The examiner respectfully submits that the term pathogen encompasses more than an organism; and that molecules may be considered pathogens. Walter et al., throughout the publication, abstract, and at para 1, teach measuring pathogen genomic sequences, particularly of Mycobacterium tuberculosis, and teach a fluorescence correlation spectroscopy method employing fluctuation autocorrelation (p. 12805) for assaying the pathogen. FCS methods inherently employ fluctuation analysis, as stated in the instant specification in the Summary of the Invention. Furthermore, the claims are drawn to assaying for a pathogen. Such identification is possible from components of a pathogen.

Appellant argues that Weiner does not teach analysis of diffusion or flow of a pathogen through a subvolume. The examiner respectfully submits that Weiner teaches fluorescence correlation spectroscopy (FCS) comprising measuring fluorescence from a volume element, reading on measuring the fluorescence from a subvolume of said sample, (see p. 85, second paragraph and last paragraph).

Walter et al., e.g., in the abstract, teach analysis for 30 seconds. Walter, at p. 12810, para 2, teaches multiplex analysis with different labeled probes, which read on a plurality of unique fluorescently-tagged probes.

Appellant's arguments regarding claim 66 are persuasive, and the instant rejection of claim 66 over Walter is withdrawn.

(9) Claim Rejections - 35 USC § 103

8. Claims 59-66 and 118-125, 127, 128, 130-138 are rejected under 35 U.S.C. 103(a) as being unpatentable by **Kask**, US 6,515,289, in view of **Lahiri et al.**, US 2003/0138853 A1.

Kask, US 6,515,289, throughout the patent, and at col. 1, lines 5-13, teaches methods of detecting substances in a sample, said method comprising: exciting a sample with radiation, (Kask at col. 3, line 63-col. 4, line 9), said sample comprising a labeled reactant that binds to a substance, reading on at least one probe capable of binding a predetermined component, and at least one fluorescent tag (col. 8, lines 8-29); Kask at, e.g., col. 2, lines 47-63, teaches monitoring intensity fluctuations of radiation emitted by molecules in a measurement volume, reading on measuring the fluorescence from a subvolume of said sample and analyzing the fluctuations of said fluorescence; and determining the presence or absence of said component, including viruses and bacteria, (col. 6, lines 31-48; and as in claims 65 and 66).

Kask at col. 1, lines 23-teach that spectroscopic methods for measuring fluorescence fluctuations are employed in fluorescence correlation spectroscopy (FCS). In considering the disclosure of the instant application in regards to measuring fluctuations in fluorescence intensity in fluorescence correlation spectroscopy, the instant specification states:

> Fluorescence correlation spectroscopy (FCS) is a single molecule detection method that measures the fluctuations in fluorescence intensity in a small (e.g., femtoliter) confocal volume. FCS employs a tightly focused laser beam to define the confocal volume. The diffusion of fluorescently labeled particles into and out of the illuminated volume determines the fluorescence intensity fluctuation patterns. From this data, one can extract both qualitative information and quantitative information on the molecule being studied. Such qualitative information includes, e.g., the presence or absence of molecular interaction; such quantitative information includes diffusion time, stoichiometry of the interactions, concentration of the interacting particles and the kinetics of the interaction.

Specification at pp. 1-2, bridging paragraph.

Kask, at col. 8, lines 9-50, teaches a plurality of primers labeled with different dyes, reading on a plurality of unique fluorescently tagged probes, as in claims 62 and 63. Kask at, e.g., col. 5, line 65-col. 6, line 3, teach cross-correlation and auto-correlation functions, and combinations thereof, as in claim 64.

Kask et al. do not teach the detection of pathogens.

Lahiri et al., US 2003/0138853 A1, throughout the publication, and at para [0077] teach assay for the presence of a pathogen for diagnosis; and at

para [0071], teaches using fluorescence correlation spectroscopy (FCS) as a detection method.

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have made and used a method of assaying for the presence of a pathogen component in a sample using fluorescence fluctuation methods, such as FCS.

One of ordinary skill in the art would have been motivated to make and use a method of assaying for the presence of a pathogen component in a sample by measuring fluorescence fluctuation, because Lahiri et al. teach using FCS for detecting pathogens for diagnosis and because Kask, at col. 7, lines 37-42, teach using FCS for high throughput screening, and for diagnostic purposes, and teaches the detection of viruses and bacteria, as stated above.

One of ordinary skill in the art would have had a reasonable expectation of success in assaying for the presence of a pathogen by measuring fluorescence fluctuations because Kask et al. teach measuring bacteria and virus by such methods.

Response to Arguments, Mailed 4/26/2007

Appellant argues that a prima facie case of obviousness has not been made because the references do not describe all elements, in particular, the references do not disclose pathogens. Appellant argues that the reference of Lahiri et al. does not explain what is meant by "derived from" a body fluid. Appellant argues that the term "derived from" does not inherently mean that the

sample includes a pathogen. Furthermore analytes indicative of pathogens could be, for example, antibodies to the pathogen, and not pathogens.

Appellant's arguments, entered 10/23/2006, have been fully considered but they are not persuasive.

Firstly, Lahiri et al., US 2003/0138853 A1, throughout the publication, and at para [0077] teach assay for the presence of a pathogen for diagnosis; and at para [0071], teaches using fluorescence correlation spectroscopy (FCS) as a detection method. Appellant's argument ignores the plain meaning of the reference.

Claims must be given their broadest reasonable interpretation consistent with the supporting description. In re Hyatt, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). The claims are drawn to pathogens. See, *e.g.*, *Invitrogen Corp v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 1997); and MPEP 211.03. The claims and the specification do not provide a limiting definition for the term "pathogen". Dorlands's Illustrated Medical Dictionary, Twenty-fifth Edition, Saunders, Philadelphia (1979) at p. 1148, defines the term pathogen as "any disease-producing microorganism **or material**." Emphasis added. Therefore, the examiner respectfully submits that the term pathogen, when given its broadest reasonable interpretation, is taught by the combination of the references of Kask and Lahiri et al.

Response to Arguments after Final Rejection

Appellant's arguments, entered 6/26/2007, have been fully considered but they are not persuasive. Appellant argues that Kask fails to teach analyzing fluctuation in fluorescence of a pathogen. However, Kask teach units of a sample that can be bacteria and viruses, and claims such in dependent claim 6, 27, 49, and 72. Kask claims fluctuation analysis in claims 1, 7, 28, 45, 50, 67, 68, and 73. Thus, the examiner respectfully submits that an argument that these elements are merely items of a laundry is not persuasive.

Lahiri et al., is cited for detection of pathogens.

Kask, at least in the Brief Summary of the Invention, teach autocorrelation analysis. Kask, e.g., at col. 11, lines 19-23, provide a example of FCS analysis for rhodamine, wherein the data collection time is 60 seconds, reading on and suggesting analysis of seconds.

Thus the features of the claimed invention were known in the art at the time of claimed invention. Methods to combine, i.e., to use bacteria, as taught by Kask, that were pathogens, as taught by Lahiri, were also familiar in the prior art. The use of bacteria that were also pathogens, would be predictable, in the outcome, as there is no structural feature to distinguish a bacteria from a pathogenic bacteria. Therefore, the examiner respectfully submits that the invention would be obvious.

The examiner respectfully notes that Claim 129 is not rejected.

(10) Response to Argument

(10) Claim Rejections - 35 USC § 112, First Paragraph

9. Claims 132-137 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is for new matter.

Response to Arguments In The Brief

Appellant argues that the application as filed conveyed to one of skill that appellant invented the claimed subject matter. Appellant argues that the decision of *In re Wertheim*, 541 F.2d 257, 265 (CCPA 1976) is relevant to the claimed invention, and that the rejection should be reversed. Appellant argues that the application provides support for a method of analyzing that occurs over a period of seconds, a period of at least 15 seconds and a period of at least 30 seconds, as shown in Examples 1-4 and Figures 1A, 2A, 3A and 4A.

The examiner respectfully submits that appellant's arguments are not persuasive. The examiner respectfully would distinguish *In re Wertheim* from the instant application. The claim at issue in *Wertheim* taught a method comprising a continuous sheet of frozen coffee extract foam that could be broken into fragments suitable for grinding particles of a particle size preferably at least 0.25

mm and freeze drying the ground frozen foam. The application in *Wertheim* taught a continuous rigid sheet that could be broken up and ground to a particle.

The particles of *Wertheim* are exemplified as to preferred dimensions and the grinding of particles to a particular size could be accomplished with predictable success. The examiner respectfully submits that a person of skill in the art would envision the full genus of particle sizes from ground fragments of frozen coffee extract sheets an not open-ended because a ground particle of coffee must be smaller than the fragment of the sheet of coffee from which it was ground.

In the instant case, however, the genus of duration of analysis in the claimed invention cannot be envisioned by one of skill in the art. Figures 1A, 2A, 3A and 4A provide the only support for durations of seconds, as in the instant claims. This support is not literal, but to be found in inspection and interpretation of the said Figures. Figure 1A, Example 1, does not show crosscorrelation between channels 1 and 2 and are disclosed to suggest that antibody does not bind to the bacteria. Figures 2A and 3A are disclosed to show crosscorrelation experimental data with peaks a approximately 27 seconds and 45 and 54 seconds. Figure 4A is disclosed to show autocorrelation experimental data with peaks mainly around 10-15 seconds.

The examiner respectfully submits the species of data peaks disclosed are not sufficient to adequately represent the claimed genus because one of skill in the art would not be apprised of the that the experimentally determined durations would provide support for the genus of any duration time of at least 15 or 30

seconds, as in the instant claims. The disclosed durations of the Figures and Examples are experimentally determined and are not within the discretion of the practitioner, unlike, for example, the particle dimensions of ground coffee. Absent evidence to the contrary, the correlation times for detecting binding are not predictable. Appellant's claim reaches through to results not possessed. Therefore the examiner respectfully submits that one of skill in the art would not envision that appellant had possession of the newly claimed invention.

(10) Claim Rejections - 35 USC § 112, Second Paragraph

10. Claims 59, 118-121, 124-126, 130-132, 134 and 136 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which appellant regards as the invention.

Response to Arguments In The Brief

Appellant argues that it is clear that the method steps set forth in the body of claim 59 could only be for the method recited in the preamble, i.e., a method of assaying for a pathogen in a sample.

Appellant's arguments are not persuasive. The examiner respectfully submits that the steps of claim 59, such as the ultimate step of analyzing the fluctuations of fluorescence, can be for purposes other than assaying for a pathogen in a sample.

The Specification states:

> The method determines the presence or absence of binding between a member (or members) of the library and a probe (or probes) by analyzing the fluctuations in fluorescence emitted by a subvolume of the sample. **Analysis of the measured fluctuations can provide information about various properties of the sample including, e.g., the presence or absence of binding between the probe and a member, the number of binding sites available on a member, diffusion coefficients, diffusion time, number of fluorescently tagged complexes present in the subvolume of the sample, the number of members to which a probe binds in a sample, counts per member, average intensity, aggregation state chemical concentration, chemical reaction kinetics, stoichiometry and combinations thereof.** These properties can be determined for members in solution, as well as in the plasma membrane of a living cell.
>
> The method **can also be used to assay for** molecular interactions between an unknown target and a probe in a sample that includes at least one probe, at least one unknown target and at least one fluorescent tag, and to determine the presence or absence of binding between a probe and an unknown target by **analyzing the fluctuations in fluorescence** emitted by a subvolume of the sample.

Specification at p. 18, lines 1-16, (emphasis added).

Thus the Specification contemplates many uses of analyzing the fluctuations of fluorescence that are not drawn to assaying for a pathogen in a sample. The examiner respectfully notes that the claims do not require that the probe be directed to or specific for the at least one pathogen. Therefore, the examiner respectfully submits that one of skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention.

11. Claims 131-133 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which appellant regards as the invention.

Response to Arguments In The Brief

In regard to claim 131, appellant argues that the term "unknown" is well-known throughout all fields of science. Appellant states that that the phrase "identity of said pathogen is unknown" refers to a fact and not a mental step. Appellant provides an example of testing a city's tainted water supply where the identity of the pathogen is unknown at the time the method is conducted.

Appellant's arguments are not persuasive. It unclear as to who or what the identity of the pathogen is "unknown" or the distinguishing physical feature of a pathogen that is unknown. It is not disputed that appellant may be their own lexicographer. The examiner does not argue that the term is repugnant to the usual usage in the art. Rather, it is that claim 131 does not reasonably apprise of one skill in the art as to the metes and bounds of the claimed invention.

In regard to the rejection of claims 132 and 133, appellant argues that a second is a known unit of time and that there is nothing indefinite about a second or a period of seconds. Appellant argues that the claim means that an analysis that occurs in less a second, or over a period of one second, does not fall within the claims. Appellant argues that the practitioner would understand the metes and bounds of the claimed invention.

Appellant's arguments are not persuasive. Claims 132 and 133 recite the limitation wherein the analyzing occurs over a period of seconds, which renders the claims vague and indefinite, because the limitation is tantamount to claiming that the analyzing occurs over a period of time, and so would not apprise one of skill in the art of the metes and bounds of the claimed invention.

(10) Claim Rejections - 35 USC § 102

12. Claims 59-66 and 118-125, 127, 128, 130-133, and 138 are rejected under 35 U.S.C. 102(e) as being anticipated by Rigler et al., US 6,582,903 B1.

Response to Appellant's Arguments In The Brief

Appellant argues that Rigler et al. do not teach each and every element of the claimed inventions.

In regard to independent claim 59, appellant argues that a pathogen must be an organism and that Rigler et al., '903 Patent, is not interested in analyzing pathogens.

Appellant quotes from their own Specification:

> Other suitable targets include organisms including e.g., pathogens (e.g., bacterial, viral, rickettsia), pathogen components, toxins, and macromolecules associated with an organism. Examples of pathogen components include pathogens, pathogen fragments, pathogen nucleic acids, pathogen proteins, pathogen carbohydrates, pathogen spores, pathogen toxins, metabolic products of pathogens, and combinations thereof.

Specification at p. 33, lines 5-6. Appellant argues that the cited paragraph clearly demonstrates the appellant's intention that the term "pathogen" refers to an "

organism", "and to convey the idea that while a pathogen necessarily includes a component of a pathogen, a component of a pathogen is not inherently a pathogen or an organism", (Brief at p. 18).

Appellant argues that "Rigler et al. are interested in activity that is happening at the receptors of the cell and analyzes various segments of the membrane to study this activity". Appellant argues that "Rigler look at activity that is occurring on cell receptors and membranes --not at the activity of entire organisms, (Brief at p. 19)." Therefore, appellant argues, "the mere use of the terms 'pathogen', 'virus' and 'bacterium' in Rigler et al. does not constitute a teaching of a method that includes analyzing the fluctuations of the fluorescence due to diffusion or flow of a pathogen through a subvolume."

In regard to claim 60, appellant argues that Rigler et al. do not teach determining the presence or absence of a pathogen in a sample, but instead teach analyzing molecules and molecular interactions. Appellant states: "Molecules are not pathogens", (Brief at p. 20). Appellant argues that the Rigler et al. method is applicable to DNA/RNA analysis; that DNA, itself, is not a pathogen, and analyzing DNA does not inherently constitute identifying the presence or absence of a pathogen.

In regard to claim 120, appellant argues that Rigler et al. do not teach a probe that includes multiple binding sites for a pathogen.

In regard to claim 121, appellant argues that Rigler et al. do not teach a pathogen that includes multiple binding sites for binding a probe.

In regard to claim 127, appellant argues that Rigler et al. do not teach obtaining a measured correlation function of a pathogen and applying a correction algorithm to the measured correlation algorithm.

In regard to claim 132 and 133, appellant argues that Rigler does not expressly teach analyzing the fluctuations in fluorescence due to diffusion or flow of a pathogen through a subvolume of a sample. In addition, appellant argues that Rigler et al. fail to teach analyzing the fluctuations in fluorescence due to diffusion or flow of a pathogen through a subvolume of a sample over a period of seconds. Appellant argues that the examiner cites no authority for the positions that "a period of seconds" encompasses time periods less than one second.

In regard to claim 138, 62 and 118, appellant argues that Rigler et a. do not teach a sample that includes a plurality of unique fluorescently tagged probes each of which is capable of binding to a unique pathogen, as in claim 138.

Appellant's arguments have been fully considered but the examiner respectfully submits that these arguments are not persuasive.

In regard to the nature of the claimed invention, the examiner respectfully notes that the first sentence of the Detailed Description section of the instant Specification states:

> **The present invention provides a method of screening** members of a library (e.g., proteins produced from a cDNA library) **using fluorescence correlation spectroscopy**. The method includes screening a sample that includes a sub-volume of the library, at least one probe and at least one fluorescent tag to determine whether a probe binds to a member of the library under equilibrium conditions.

Specification at p. 17, lines 23-27, (emphasis added). Thus the present invention of the application uses the method of fluorescence correlation spectroscopy (FCS).

The examiner respectfully notes that the instant Specification teaches:

> **Fluorescence correlation spectroscopy (FCS) is a single molecule detection method that measures the fluctuations in fluorescence intensity in a small (e.g., femtoliter) confocal volume.** FCS employs a tightly focused laser beam to define the confocal volume. The diffusion of fluorescently labeled particles into and out of the illuminated volume determines the fluorescence intensity fluctuation patterns. From this data, one can extract both qualitative information and quantitative information on the molecule being studied. Such qualitative information includes, e.g., the presence or absence of molecular interaction; such quantitative information includes diffusion time, stoichiometry of the interactions, concentration of the interacting particles and the kinetics of the interaction.

Specification at pp. 1-2, bridging paragraph, (emphasis added). Thus fluorescence correlation spectroscopy is a long established procedure that measures fluctuations in fluorescence intensity.

The examiner respectfully notes that in subsection III.A. the Specification states:

> A. PROBES FOR PATHOGEN DETECTION
>
> **Various probes can be prepared for use in detecting pathogens. Antigens of the pathogens, for example, can be detected using specific antibody probes and nucleic acid sequences of the pathogen can be detected using specific oligonucleotide probes.** The probes preferably are selected to target glycoproteins, proteins, nucleic acids, or combinations thereof, which may include specific portions of the pathogen, a spore of the pathogen, toxins, metabolic products of the pathogen, biological responses induced by the pathogen. The specific probe-sets can be prepared based on genomic data, the characterization

> of the expressed proteome, and clinical data on outcomes of infection.
>
> Oligonucleotide probes can be designed based on information obtained using Polymerase Chain Reaction, PCR, and the analysis of genomic data for variable and conserved regions of DNA in related pathogen species. Antibody probes can be designed for unique antigens expressed by specific pathogens as determined by genomic and proteomic database analysis. **Pathogenic virulence can often be traced to unique expression of one or more proteins or glycoproteins. Such unique expression of one or more proteins or glycoproteins can serve as a specific probe target.**

Specification at p. 30, lines 15-30. Thus the Specification contemplates the detection of pathogens using antibody or oligonucleotide probes, which detect, for example, antigens or nucleic acid sequences, respectively, of the pathogens.

The examiner respectfully notes that the Specification states:

> IV. THE TARGET
>
> The target can include any target of interest. The target can be unknown or known. Unknown targets include those targets to which it is not known whether or not the probe binds. Known targets include those targets to which a binding site of a probe of interest binds. **Examples of suitable targets include macromolecules (e.g., proteins, peptides, polynucleic acids, and polysaccharides), molecules (e.g., amino acids, nucleic acids, and saccharides), and combinations thereof. Useful macromolecules include, e.g., antibodies, receptor proteins, lectins, hormones, protein A, protein G, avidin, enzymes, and combinations thereof.**
>
> The target can be a library, a portion of a library, a member of a library or a combination thereof. Suitable libraries include, e.g., apatamer libraries, phage display libraries, antibody libraries, peptide libraries, and translated cDNA libraries. Examples of members of a library include proteins, peptides, polynucleic acids, organic polymers, polysaccharides, amino acids, nucleic acids, and saccharides.

Specification at p. 31, line 26-p. 32, line 8, (emphasis added). Thus the Specification teaches that the target can include those targets to which a binding site of a probe of interest binds; and that targets of the instant invention include proteins, peptides, nucleic acids, etc.

Appellant's arguments have been considered but are not persuasive. Firstly, as stated in the previous Office action, claims must be given their broadest reasonable interpretation consistent with the supporting description. In re Hyatt, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). The claims are drawn to assaying for a pathogen in a sample. See, *e.g.*, *Invitrogen Corp v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 1997); and MPEP 211.03.

For the purpose of construing claims, the Specification states:

> Other suitable targets include **organisms including e.g., pathogens (e.g., bacterial, viral, rickettsia), pathogen components**, toxins, and macromolecules associated with an organism. Examples of **pathogen components include pathogens, pathogen fragments, pathogen nucleic acids, pathogen proteins**, pathogen carbohydrates, pathogen spores, pathogen toxins, metabolic products of pathogens, and combinations thereof.

Specification at p. 33, lines 5-9, (emphasis added). The instant Brief, at p. 18, quotes this paragraph. The examiner respectfully submits that this passage is not straightforward. The initial sentence of this passage states that "targets" include "organisms" that include, for example, pathogens, such as bacteria, viruses and rickettsia. However this sentence also states that organisms include "pathogen components", "toxins" and "macromolecules associated with an

organism". The aforementioned passage further provides examples of the said "pathogen components", that include pathogens, pathogen proteins and pathogen nucleic acids. Thus the Specification teach organisms as including pathogen components that are pathogen protein and pathogen nucleic acids, for example. Therefore, the examiner respectfully submits that appellant's reading of the term "pathogen" as necessarily drawn to "organisms" can be taken to mean that the term "pathogen" includes pathogen fragments, pathogen nucleic acids, pathogen proteins, et cetera.

The examiner further respectfully submits that appellant's arguments place too restrictive an interpretation of the claim term "pathogen". The Specification does not appear to provide a limiting definition of the term pathogen, which provides bacteria and viruses as *examples* of pathogens, including the specific example of the bacterial genus rickettsia. The examiner respectfully submits that the claim term "pathogen", given its broadest interpretation consistent with the Specification, can include pathogen components, pathogen fragments, pathogen nucleic acids, pathogen proteins, pathogen carbohydrates, pathogen spores, pathogen toxins, metabolic products of pathogens, and combinations thereof.

Secondly, the examiner respectfully submits that one of ordinary skill in the art would understand the term pathogen as to not be restricted to microorganisms. As stated in the previous Office actions, Dorlands's Illustrated Medical Dictionary, Twenty-fifth Edition, Saunders, Philadelphia (1979, of

record), at p. 1148, defines the term pathogen as "any disease-producing microorganism **or material**", (emphasis added).

Furthermore, the instant Specification, e.g., at p. 31, lines 6-7, teaches that "[t]he probes can be designed to detect the pathogen, toxins secreted by the pathogen and combinations thereof." The instant Specification at p. 31, lines 14-15, states that "[p]robes can be designed to specifically bind target DNA sequences and target viral coat proteins". Thus, the examiner respectfully submits that the instant Specification contemplates toxins and viral DNA as examples of disease-producing materials that are pathogens.

Also, Rigler et al., state

> The method according to the invention allows for the measurement of molecular and /or **cellular** mobilities in an especially advantageous way. Such determinations are of great interest in technical, biological and **medical** terms . . . Preferably, this is done by labeling the **cells**, molecular complexes or molecules of interest with specific dye-labeled ligands, such as labeled antibodies or antibody derivatives, or by direct labeling with a dye label.

Rigler et al., at col. 21, line 63-col. 22, line 11, (emphasis added). Thus Rigler et al. teach detecting cells by detecting molecules on or in those cells. Rigler et al. teach the detection of cells, which can be pathogens, for medical reasons.

Rigler et al., at col. 11, lines 51-54, teach that nucleic acids can be pathogens and state that analytes, such as homologous nucleic acid sequences can be dramatically different with respect to their biological activities, such as e.g. their own pathogenicity or the pathogenicities of their product.

Furthermore, Rigler et al. at col. 38, line 29-col. 39, line 32, teach the detection of single bacteria through the binding specificities of surface-expressing bacteria. Rigler et al. state:

> The use of the methodology described of functional assignment of genetically encoded **peptide segments** will become very important especially in **allergologic research**. The assignment of immuno-dominant epitopes on allergens (e.g. Aspergillus, milk protein, α-amylase) is of extraordinary importance and represents a problem that has been difficult to solve to date. Typical problems occurring in practice are:
>
> The determination of the **IgE** binding molecules in a mixture of substances which is usually ill-characterized. For instance, answering to the question is important which contents of soya lecithin are **immunogen**: the pure substance alone, the pure substance in its interaction with impurities of the preparation, or the interaction with structures of the **host** organism. According to the invention, the different substances in the mixture can be differentiated with labeled IgE from **patients**.
>
> By expression of subgenic gene segments, the immunodominant epitopes can be localized and characterized by the method mentioned above. With these results, evolutively analogue functional molecules lacking the corresponding immunodominant regions, e.g. a **less immunogenic** α-amylase, can be generated by the methods described in WO92/18645, and the specific epitopes can be prepared simply by standard methods of genetic engineering and be used as pure test reagents or for **desensibilization**.

Rigler et al. at col. 39, lines 6-32. Thus Rigler et al., consider assaying of allergens, which read on pathogens, because allergies are disease.

Therefore, the examiner respectfully submits that one of ordinary skill in the art would understand the term pathogen as to not be restricted to microorganisms.

Thirdly, the examiner respectfully notes that the appellant agrees that Rigler et al. disclose the terms “pathogen,” "virus" and "bacterium", (Brief at p. 19; see also Rigler et al., e.g., at col. 25, lines 10-25, col. 35, lines 57-65). However, appellant argues that Rigler does not teach the analysis of these pathogens, viruses and bacteria by a method that includes analyzing the fluctuations of fluorescence due to diffusion or flow through a subvolume, (Brief at p. 19).

However, as stated in the previous Office actions, Rigler et al., e.g., at col. 1, lines 55-58, teach fluorescence correlation spectroscopy (FCS) using chromophorous molecular structures having fluorescence properties, reading on fluorophores; wherein the fluorophorous molecules in solution are exposed to the intense exciting light of a laser, (Rigler et al. at col. 2, lines 21-24). As discussed, immediately above, the instant Specification notes that fluorescence correlation spectroscopy (FCS) is a single molecule detection method that measures the fluctuations in fluorescence intensity in a small (e.g., femtoliter) confocal volume.

Rigler et al., at col. 1, lines 55-164, state that the invention of Rigler et al. “is based on a luminescence detection and makes use of a technique which is known per se under the name of fluorescence correlation spectroscopy (FCS). Chromophorous molecular structures having fluorescence properties that can be used to obtain information about the molecular environment of a chromophorous ligand.” Rigler et al., at col. 21, lines 16-23, teach their invention as applicable to molecules that do not fluctuate or fluctuate very slowly, as in cases involving cells.

Appellant argues that Rigler et al. looks at "activity occurring on cell receptors and membranes and "not at the activity of entire organisms", it is again respectfully noted that the instant Specification teaches the use of oligonucleotide and antibody probes. The instant Specification, at p. 32, teaches receptor proteins as suitable targets. It is usual in the art to detect pathogens by the use of probes to molecules, as taught by the instant Specification.

In regard to looking at the "activity of entire organism", the nature of the "activity" is not specified. It is noted that claim 59 does not require that the specificity of the probe be specified. If appellant is referring to the activity of pathogenicity itself, it is well-known in the art, that the capacity of a disease-producing microorganism or material to actually be pathogenic also involves the particularities of the subject having the disease. The reference of Robbins and Cotran, Pathologic Basis of Disease, Second Edition, W.B. Saunders Co., Philadelphia, (1979, of record), at pp. 22-26, teach numerous pathogens, including biologic agents. Robbins et al., at p. 25, stress that, for example, whether an agent is a pathogen, is dependent not only upon the virulence of the agent itself, but also the susceptibility of the host. If appellant's arguments are drawn to pathogens as the causative agent of disease, then the examiner respectfully notes that the measurement of fluctuations of fluorescence, as in fluorescence correlation spectroscopy, do not characterize the interaction of the host with the pathogen.

In regard to claim 120, appellant argues that Rigler et al. do not teach a probe that includes multiple binding sites for a pathogen.

Rigler et al., at col. 37, lines 34-37, teach complexed ligands coupled to a fluorescence label, which read on a probe that includes multiple binding sites. Rigler et al., as explained above, teach the targeting of pathogens.

In regard to claim 121, appellant argues that Rigler et al. do not teach a pathogen that includes multiple binding sites for binding a probe.

Rigler et al., at col. 11, line 45-col. 12, line 22, in section 3, "Cross Correlation", teach increasing detection specificity by simultaneously binding of at least two differently labeled test reagents to one analyte, which reads on targets that include multiple binding sites for the probe, (it is noted that claim 121 is dependent on claim 59, which is drawn to "at least one probe").

In regard to claim 127, appellant argues that Rigler et al. do not teach obtaining a measured correlation function of a pathogen and applying a correction algorithm to the measured correlation function.

Rigler et al., at col. 12, lines 5-10, state: "By means of time cross correlation of the fluorescence signals detected according to the invention, the signals of the uncorrelated free test reagents can be efficiently suppressed at the level of electronic signal processing." The examiner respectfully submits that this reads on a method of obtaining a measured correlation function of a pathogen and applying a correction algorithm.

In regard to claim 132 and 133, appellant argues that Rigler et al. do not expressly teach analyzing the fluctuations in fluorescence due to diffusion or flow of a pathogen through a subvolume of a sample. In addition, appellant argues that Rigler et al. fail to teach analyzing the fluctuations in fluorescence due to diffusion or flow of a pathogen through a subvolume of a sample over a period of seconds. Appellant argues that the examiner cites no authority for the positions that "a period of seconds" encompasses time periods less than one second.

Firstly, Rigler et al. teach fluorescence correlation spectroscopy, (FCS), which analyzes fluorescence fluctuation through a volume and teach the use of FCS to assay pathogens, as discussed above.

Secondly, Rigler et al. contemplate measuring dwelling times that occur over a range of seconds. Rigler et al. state:

> Life of Complexes During Measurement
>
> A complex of a target molecule to be detected and a labeled test reagent is detectable according to the invention only in the case that the complex remains stable throughout the **measuring time**. This would not be the case anymore with average complex dwelling times in large volume elements **in the range of seconds, if the complexes themselves had a decay time in the range of seconds**. This can thoroughly be the case with biologically relevant reactions such as metal ion complexations in which binding constants of 10^6 $l \cdot mol^{-1}$, for example, are relevant. The small volume elements according to the invention, however, mean so short average dwelling times (<1 ms) that for virtually all interesting complexation reactions a complex will remain stable throughout its dwelling time in the measuring volume.

Rigler et al. at col. 7, lines 13-27.

Thirdly, it is respectfully noted by the examiner that instant claims 132 and 133 are drawn to "analyzing" the fluctuations of fluorescence that occurs over a period of seconds. The claims do not specify that the period of time for coincident peaks occur over a period of seconds, (see e.g., the instant Specification at Examples 1-4).

Fourthly, usage of the term seconds to describe fractions of a single second, such as 0.5 seconds, is not uncommon. The instant Specification does not provide a limiting definition of the term "seconds". The figures of the instant Specification, which appellant depend upon for support for the term, show fractions of seconds in the abscissa.

Rigler state:

> The possibility to determine diffusion times in terms of **fractions of seconds** allows to analyze the kinetic interaction of two molecules with high association constants and to determine recombination and dissociation rate constants. This is of special interest for the characterization of the interactions having high biological specificity, such as antigen/antibody, ligand/receptor, and the like interactions. Analysis of particularly slow processes with constants up to 10^{-6} s^{-1} is easily possible due to the advantage of self-calibration inherent to the method according to the invention (FIG. 19).

Rigler et al. at col. 23, line 59-col. 24, line 4. Thus Rigler uses the term "seconds" to refer to fractions of seconds.

In regard to claim 138, 62 and 118, appellant argues that Rigler et al. do not teach a sample that includes a plurality of unique fluorescently tagged probes each of which is capable of binding to a unique pathogen, as in claim 138.

Rigler et al. at col. 11, lines 33-44, teach parallel determination of at least two different analytes in a sample, wherein a plurality of fluorescently tagged probes are used to detect several targets in one sample; and which describes a sample that includes a plurality of unique fluorescently tagged probes each of which is capable of binding to a unique pathogen.

13. Claims 59-64, 66 and 118-125, 127, 128, 130-133, and 138 are rejected under 35 U.S.C. 102(b) as being anticipated by Rigler, Journal of Biotechnology, vol. 41 (1995), pp. 177-186.

Response to Arguments In The Brief

Appellant argues that Rigler (1995) does not teach each and every element of the claimed inventions.

In regard to independent claim 59, appellant argues that a pathogen must be an organism and that Rigler (1995) is not interested in analyzing pathogens. Appellant argues that there is no evidence of record that single stranded M13 bacteriophage DNA, itself, produces a disease, (Brief at p. 25). Appellant argues that the term "pathogen" refers to an " organism", (Brief at p. 25). Appellant argues that Rigler (1995) is not interested in analyzing the fluctuations of fluorescence due to diffusion or flow of a pathogen through a subvolume, (Brief at p. 25).

In regard to claim 60, appellant argues that Rigler (1995) does not teach a probe capable of binding a pathogen. Appellant argues that Rigler (1995)

discloses that FCS can be used to analyze interactions between ligands and target molecules that in size, including DNA-primer. Appellant argues DNA-primers are not inherently probes capable of binding a predetermined pathogen, (Brief at p. 26).

In regard to claims 66 and 130, Rigler (1995) does not teach a virus. Appellant argues that Rigler (1995) also does not analyze fluctuations of fluorescence that are due of the diffusion or flow of a virus through a subvolume. Rigler (1995) is directed to single molecule detection, as indicated by the title of the Rigler reverence ("Fluorescence correlations, single molecule detection and large number screening"). Appellant quotes from Rigler (1995) to show that Rigler (1995) analyzes labeled DNA or RNA and not the virus itself.

In regard to claim 120, appellant argues that Rigler (1995) does not teach a probe that includes multiple binding sites for a pathogen.

In regard to claim 121, appellant argues that Rigler (1995) does not teach a pathogen that includes multiple binding sites for binding a probe.

In regard to claim 127, appellant argues that Rigler (1995) does not teach obtaining a measured correlation function of a pathogen and applying a correction algorithm to the measured correlation algorithm.

In regard to claim 132 and 133, appellant argues that Rigler (1995) does not expressly teach analyzing the fluctuations in fluorescence due to diffusion or flow of a pathogen through a subvolume of a sample. In addition, appellant argues that Rigler et al. fail to teach analyzing the fluctuations in fluorescence due to diffusion or flow of a pathogen through a subvolume of a sample over a

period of seconds. Appellant argues that the examiner cites no authority for the positions that "a period of seconds" encompasses time periods less than one second.

In regard to claim 138, 62 and 118, appellant argues that Rigler (1995) does not teach a sample that includes a plurality of unique fluorescently tagged probes each of which is capable of binding to a unique pathogen, as in claim 138.

Appellant's arguments have been fully considered but the examiner respectfully submits that these arguments are not persuasive.

In regard to the nature of the claimed invention, the examiner respectfully notes that the first sentence of the Detailed Description section of the instant Specification states:

> **The present invention provides a method of screening** members of a library (e.g., proteins produced from a cDNA library) **using fluorescence correlation spectroscopy**. The method includes screening a sample that includes a sub-volume of the library, at least one probe and at least one fluorescent tag to determine whether a probe binds to a member of the library under equilibrium conditions.

Specification at p. 17, lines 23-27, (emphasis added). Thus the present invention of the application uses the method of fluorescence correlation spectroscopy (FCS).

The examiner respectfully notes that the instant Specification teaches:

> **Fluorescence correlation spectroscopy (FCS) is a single molecule detection method that measures the fluctuations in fluorescence intensity in a small (e.g., femtoliter) confocal**

> **volume.** FCS employs a tightly focused laser beam to define the confocal volume. The diffusion of fluorescently labeled particles into and out of the illuminated volume determines the fluorescence intensity fluctuation patterns. From this data, one can extract both qualitative information and quantitative information on the molecule being studied. Such qualitative information includes, e.g., the presence or absence of molecular interaction; such quantitative information includes diffusion time, stoichiometry of the interactions, concentration of the interacting particles and the kinetics of the interaction.

Specification at pp. 1-2, bridging paragraph, (emphasis added). Thus fluorescence correlation spectroscopy is a long established procedure that measures fluctuations in fluorescence intensity.

The examiner respectfully notes that in subsection III.A. the Specification states:

> A. PROBES FOR PATHOGEN DETECTION
>
> **Various probes can be prepared for use in detecting pathogens. Antigens of the pathogens, for example, can be detected using specific antibody probes and nucleic acid sequences of the pathogen can be detected using specific oligonucleotide probes.** The probes preferably are selected to target glycoproteins, proteins, nucleic acids, or combinations thereof, which may include specific portions of the pathogen, a spore of the pathogen, toxins, metabolic products of the pathogen, biological responses induced by the pathogen. The specific probe-sets can be prepared based on genomic data, the characterization of the expressed proteome, and clinical data on outcomes of infection.
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> Oligonucleotide probes can be designed based on information obtained using Polymerase Chain Reaction, PCR, and the analysis of genomic data for variable and conserved regions of DNA in related pathogen species. Antibody probes can be designed for unique antigens expressed by specific pathogens as determined by genomic and proteomic database analysis. **Pathogenic virulence can often be traced to unique expression of one or more proteins or glycoproteins. Such unique expression of one or**

> **more proteins or glycoproteins can serve as a specific probe target.**

Specification at p. 30, lines 15-30. Thus the Specification contemplates the detection of pathogens using antibody or oligonucleotide probes, which detect, for example, antigens or nucleic acid sequences, respectively, of the pathogens.

The examiner respectfully notes that the Specification states:

> IV. THE TARGET
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> The target can include any target of interest. The target can be unknown or known. Unknown targets include those targets to which it is not known whether or not the probe binds. Known targets include those targets to which a binding site of a probe of interest binds. **Examples of suitable targets include macromolecules (e.g., proteins, peptides, polynucleic acids, and polysaccharides), molecules (e.g., amino acids, nucleic acids, and saccharides), and combinations thereof. Useful macromolecules include, e.g., antibodies, receptor proteins, lectins, hormones, protein A, protein G, avidin, enzymes, and combinations thereof.**
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> The target can be a library, a portion of a library, a member of a library or a combination thereof. Suitable libraries include, e.g., apatamer libraries, phage display libraries, antibody libraries, peptide libraries, and translated cDNA libraries. Examples of members of a library include proteins, peptides, polynucleic acids, organic polymers, polysaccharides, amino acids, nucleic acids, and saccharides.

Specification at p. 31, line 26-p. 32, line 8, (emphasis added). Thus the Specification teaches that the target can include those targets to which a binding site of a probe of interest binds; and that targets of the instant invention include proteins, peptides, nucleic acids, etc.

Appellant's arguments have been considered but are not persuasive. Firstly, as stated in the previous Office action, claims must be given their

broadest reasonable interpretation consistent with the supporting description. In re Hyatt, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). The claims are drawn to assaying for a pathogen in a sample. See, *e.g.*, *Invitrogen Corp v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 1997); and MPEP 211.03.

For the purpose of construing claims, the Specification states:

> Other suitable targets include **organisms including e.g., pathogens (e.g., bacterial, viral, rickettsia), pathogen components**, toxins, and macromolecules associated with an organism. Examples of **pathogen components include pathogens, pathogen fragments, pathogen nucleic acids, pathogen proteins**, pathogen carbohydrates, pathogen spores, pathogen toxins, metabolic products of pathogens, and combinations thereof.

Specification at p. 33, lines 5-9, (emphasis added). The instant Brief, at p. 18, quotes this paragraph. The examiner respectfully submits that this passage is not straightforward. The initial sentence of this passage states that "targets" include "organisms" that include, for example, pathogens, such as bacteria, viruses and rickettsia. However this sentence also states that organisms include "pathogen components", "toxins" and "macromolecules associated with an organism". The aforementioned passage further provides examples of the said "pathogen components", that include pathogens, pathogen proteins and pathogen nucleic acids. Thus the Specification teach organisms as including pathogen components that are pathogen protein and pathogen nucleic acids, for example. Therefore, the examiner respectfully submits that appellant's reading of the term "pathogen" as necessarily drawn to "organisms" can be taken to

mean that the term "pathogen" includes pathogen fragments, pathogen nucleic acids, pathogen proteins, et cetera.

The examiner further respectfully submits that appellant's arguments place too restrictive an interpretation of the claim term "pathogen". The Specification does not appear to provide a limiting definition of the term pathogen, which provides bacteria and viruses as *examples* of pathogens, including the specific example of the bacterial genus rickettsia. The examiner respectfully submits that the claim term "pathogen", given its broadest interpretation consistent with the Specification, can include pathogen components, pathogen fragments, pathogen nucleic acids, pathogen proteins, pathogen carbohydrates, pathogen spores, pathogen toxins, metabolic products of pathogens, and combinations thereof.

Secondly, the examiner respectfully submits that one of ordinary skill in the art would understand the term pathogen as to not be restricted to microorganisms. As stated in the previous Office actions, Dorlands's Illustrated Medical Dictionary, Twenty-fifth Edition, Saunders, Philadelphia (1979, of record), at p. 1148, defines the term pathogen as "any disease-producing microorganism **or material**", (emphasis added).

Furthermore, the instant Specification, e.g., at p. 31, lines 6-7, teaches that "[t]he probes can be designed to detect the pathogen, toxins secreted by the pathogen and combinations thereof." The instant Specification at p. 31, lines 14-15, states that "[p]robes can be designed to specifically bind target DNA sequences and target viral coat proteins". Thus, the examiner respectfully

submits that the instant Specification contemplates toxins and viral DNA as examples of disease-producing materials that are pathogens.

Rigler (1995), throughout the publication and abstract, and at pp. 182-184, teach methods of assaying for the presence of a pathogen component in a sample, said method comprising: exciting a sample with laser radiation, (Rigler (1995) at p. 178, Fig. 1), said sample comprising at least one probe (Rigler (1995) at p. 178, para 2) capable of binding a predetermined pathogen component, such as hepatitis B and C or HIV and virus that is M13 bacteriophage, Rigler (1995) at pp. 182-193, bridging paragraph, and as in claim 65) using several fluorescence labeled primers in the form of a cocktail, (also reading on claim 62), reading on methods comprising at least one fluorescent tag, and measuring the fluorescence fluctuations from an extremely small volume element, (Rigler (1995), at p. 177, para 1-2), which reads on a subvolume of said sample and analyzing the fluctuations of said fluorescence, and determining the presence or absence of said pathogen component, (Rigler (1995) at pp. 182-193, bridging paragraph).

Rigler (1995), at p. 182, Fig. 6, teaches cross-correlation in two colors, reading on a plurality of probes with different fluorophore tags, and e.g., at p. 180, teach autocorrelations, as in claims 62-64.

Rigler (1995), at p. 178, para 3, teach fluctuation analysis in FCS. Rigler (1995), at p. 182, column 2, discloses assaying diffusion times of viruses, (p. 182). Rigler at p. 179 teach molecular interactions determined at the cell surface of bladder carcinoma cells, which are pathogens.

Rigler (1995), at e.g., the abstract, teaches a period of milliseconds. The examiner respectfully submits that the claimed term "period of seconds" encompasses time periods of less than one second.

Rigler (1995), at p. 182, right column, teaches use of several fluorescence labeled primers in the form of a "cocktail", thereby teaching a plurality of probes.

14. Claims 59-64, 66 and 118-125, 127, 128, 130-138 are rejected under 35 U.S.C. 102(b) as being anticipated by Weiner et al., Digestion, 2000; vol. 61, pp. 84-89.

Response to Arguments In The Brief

Appellant argues that Weiner et al. do not teach each and every element of the claimed inventions.

In regard to independent claim 59, appellant argues that a pathogen must be an organism and that Weiner et al., is not interested in analyzing pathogens.

In regard to claim 60, appellant argues that Weiner et al. do not teach determining the presence or absence of a pathogen in a sample, but instead teach analyzing molecules and molecular interactions.

In regard to claims 66 and 130, appellant argues that Weiner et al. do not teach a virus. Appellant argues that Weiner et al. also do not analyze fluctuations of fluorescence that are due to the diffusion or flow of a virus through a subvolume.

In regard to claim 120, appellant argues that Weiner et al. do not teach a probe that includes multiple binding sites for a pathogen.

In regard to claim 121, appellant argues that Weiner et al. do not teach a pathogen that includes multiple binding sites for binding a probe.

In regard to claim 127, appellant argues that Weiner et al. do not teach obtaining a measured correlation function of a pathogen and applying a correction algorithm to the measured correlation algorithm.

In regard to claims 132-137, appellant argues that Weiner et al. do not expressly teach analyzing the fluctuations in fluorescence due to diffusion or flow of a pathogen through a subvolume of a sample. In addition, appellant argues that Weiner et al. fail to teach analyzing the fluctuations in fluorescence due to diffusion or flow of a pathogen through a subvolume of a sample over a period of seconds. Appellant argues that the examiner cites no authority for the positions that "a period of seconds" encompasses time periods less than one second.

In regard to claim 138, 62 and 118, appellant argues that Weiner et al. do not teach a sample that includes a plurality of unique fluorescently tagged probes each of which is capable of binding to a unique pathogen, as in claim 138.

Appellant's arguments have been fully considered but the examiner respectfully submits that these arguments are not persuasive.

In regard to the nature of the claimed invention, the examiner respectfully notes that the first sentence of the Detailed Description section of the instant Specification states:

> **The present invention provides a method of screening** members of a library (e.g., proteins produced from a cDNA library) **using fluorescence correlation spectroscopy**. The method includes screening a sample that includes a sub-volume of the library, at least one probe and at least one fluorescent tag to determine whether a probe binds to a member of the library under equilibrium conditions.

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The examiner respectfully notes that the instant Specification teaches:

> **Fluorescence correlation spectroscopy (FCS) is a single molecule detection method that measures the fluctuations in fluorescence intensity in a small (e.g., femtoliter) confocal volume.** FCS employs a tightly focused laser beam to define the confocal volume. The diffusion of fluorescently labeled particles into and out of the illuminated volume determines the fluorescence intensity fluctuation patterns. From this data, one can extract both qualitative information and quantitative information on the molecule being studied. Such qualitative information includes, e.g., the presence or absence of molecular interaction; such quantitative information includes diffusion time, stoichiometry of the interactions, concentration of the interacting particles and the kinetics of the interaction.

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> **Various probes can be prepared for use in detecting pathogens. Antigens of the pathogens, for example, can be detected using specific antibody probes and nucleic acid**

> **sequences of the pathogen can be detected using specific oligonucleotide probes.** The probes preferably are selected to target glycoproteins, proteins, nucleic acids, or combinations thereof, which may include specific portions of the pathogen, a spore of the pathogen, toxins, metabolic products of the pathogen, biological responses induced by the pathogen. The specific probe-sets can be prepared based on genomic data, the characterization of the expressed proteome, and clinical data on outcomes of infection.
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> Oligonucleotide probes can be designed based on information obtained using Polymerase Chain Reaction, PCR, and the analysis of genomic data for variable and conserved regions of DNA in related pathogen species. Antibody probes can be designed for unique antigens expressed by specific pathogens as determined by genomic and proteomic database analysis. **Pathogenic virulence can often be traced to unique expression of one or more proteins or glycoproteins. Such unique expression of one or more proteins or glycoproteins can serve as a specific probe target.**

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> apatamer libraries, phage display libraries, antibody libraries, peptide libraries, and translated cDNA libraries. Examples of members of a library include proteins, peptides, polynucleic acids, organic polymers, polysaccharides, amino acids, nucleic acids, and saccharides.

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Appellant's arguments have been considered but are not persuasive. Firstly, as stated in the previous Office action, claims must be given their broadest reasonable interpretation consistent with the supporting description. In re Hyatt, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). The claims are drawn to assaying for a pathogen in a sample. See, *e.g.*, *Invitrogen Corp v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 1997); and MPEP 211.03.

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The examiner further respectfully submits that appellant's arguments place too restrictive an interpretation of the claim term "pathogen". The Specification does not appear to provide a limiting definition of the term pathogen, which provides bacteria and viruses as *examples* of pathogens, including the specific example of the bacterial genus rickettsia. The examiner respectfully submits that the claim term "pathogen", given its broadest interpretation consistent with the Specification, can include pathogen components, pathogen fragments, pathogen nucleic acids, pathogen proteins, pathogen carbohydrates, pathogen spores, pathogen toxins, metabolic products of pathogens, and combinations thereof.

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Furthermore, the instant Specification, e.g., at p. 31, lines 6-7, teaches that "[t]he probes can be designed to detect the pathogen, toxins secreted by the pathogen and combinations thereof." The instant Specification at p. 31, lines 14-15, states that "[p]robes can be designed to specifically bind target DNA sequences and target viral coat proteins". Thus, the examiner respectfully submits that the instant Specification contemplates toxins and viral DNA as examples of disease-producing materials that are pathogens.

Weiner et al., throughout the publication, abstract, and at para 1, teach measuring serum hepatitis C virus (HCV) RNA, and teach a fluorescence correlation spectroscopy method (p. 85, Methods, para 7) for assaying the pathogen, HCV in a sample, reading on assaying for the presence of a pathogen component in a sample, said method comprising: exciting a sample with argon-ion laser, radiation, said sample comprising Cy3-labeled amplimers for HCV RNA, (Weiner et al., at p. 85, para 8), reading on a at least one probe capable of binding a predetermined pathogen component, and at least one fluorescent tag; measuring the fluorescence from a subvolume of said sample and measuring diffusion times, (p. 85, para 8), reading on analyzing the fluctuations of said fluorescence; and determining the presence or absence of said HCV.

Weiner et al., throughout the publication, abstract, and at para 1, teach measuring serum hepatitis C virus (HCV) RNA, and teach a fluorescence correlation spectroscopy method (p. 85, Methods, para 7) for assaying the pathogen that is the virus hepatitis C.

Weiner et al., at p. 85, last paragraph, teach analysis for 60 seconds. Weiner, at p. 88, para 6, teach the use of internal control RNAs labeled with different fluorochromes to be processed in the FCS assay for pathogen, thereby reading on a plurality of unique fluorescently tagged probes.

15. Claims 59-65 and 118-125, 127, 128, 130-138 are rejected under 35 U.S.C. 102(b) as being anticipated by Walter et al., Proc. Natl. Acad. Sci., USA, November 1996, vol. 93, pp. 12805-12810.

Response to Arguments In The Brief

Appellant argues that Weiner et al. do not teach each and every element of the claimed inventions.

In regard to independent claim 59, appellant argues that a pathogen must be an organism and that the genomic DNA of *Mycobacterium tuberculosis* is not an organism.

In regard to claims 60, 61-64, 122, 123, 127 and 128, appellant argues that Walter et al. do not teach determining the presence or absence of a pathogen in a sample, but instead teach analyzing molecules and molecular interactions.

In regard to claim 65, appellant argues that Walter et al. do not teach a bacterium. Appellant argues that Walter et al. also do not analyze fluctuations of fluorescence that are due to the diffusion or flow of a bacteria through a subvolume.

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In regard to claim 130, appellant argues that Walter et al. do not teach a bacterium or a virus.

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> Oligonucleotide probes can be designed based on information obtained using Polymerase Chain Reaction, PCR, and the analysis of genomic data for variable and conserved regions of DNA in related pathogen species. Antibody probes can be designed for unique antigens expressed by specific pathogens as determined by genomic and proteomic database analysis. **Pathogenic virulence can often be traced to unique expression of one or more proteins or glycoproteins. Such unique expression of one or more proteins or glycoproteins can serve as a specific probe target.**

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Specification at p. 31, line 26-p. 32, line 8, (emphasis added). Thus the Specification teaches that the target can include those targets to which a binding site of a probe of interest binds; and that targets of the instant invention include proteins, peptides, nucleic acids, etc.

Appellant's arguments have been considered but are not persuasive. Firstly, as stated in the previous Office action, claims must be given their broadest reasonable interpretation consistent with the supporting description. In re Hyatt, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). The claims are drawn to assaying for a pathogen in a sample. See, *e.g.*, *Invitrogen Corp v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 1997); and MPEP 211.03.

For the purpose of construing claims, the Specification states:

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The examiner further respectfully submits that appellant's arguments place too restrictive an interpretation of the claim term "pathogen". The Specification does not appear to provide a limiting definition of the term pathogen, which provides bacteria and viruses as *examples* of pathogens,

including the specific example of the bacterial genus rickettsia. The examiner respectfully submits that the claim term "pathogen", given its broadest interpretation consistent with the Specification, can include pathogen components, pathogen fragments, pathogen nucleic acids, pathogen proteins, pathogen carbohydrates, pathogen spores, pathogen toxins, metabolic products of pathogens, and combinations thereof.

Secondly, the examiner respectfully submits that one of ordinary skill in the art would understand the term pathogen as to not be restricted to microorganisms. As stated in the previous Office actions, Dorlands's Illustrated Medical Dictionary, Twenty-fifth Edition, Saunders, Philadelphia (1979, of record), at p. 1148, defines the term pathogen as "any disease-producing microorganism **or material**", (emphasis added).

Furthermore, the instant Specification, e.g., at p. 31, lines 6-7, teaches that "[t]he probes can be designed to detect the pathogen, toxins secreted by the pathogen and combinations thereof." The instant Specification at p. 31, lines 14-15, states that "[p]robes can be designed to specifically bind target DNA sequences and target viral coat proteins". Thus, the examiner respectfully submits that the instant Specification contemplates toxins and viral DNA as examples of disease-producing materials that are pathogens.

Walter et al., throughout the publication and abstract and at p.12805, para 1-2, teach a method of assaying for the presence of a *Mycobacterium tuberculosis* pathogen component in a sample, said method comprising: exciting a sample with laser radiation, 9P. 12805, para 1), said sample comprising at

least one primer (see Table 1, p. 12807) capable of binding a *M. tuberculosis* DNA pathogen component, and at least one fluorescent rhodamine tag; measuring the fluorescence from a investigated volume (Walter et al. at p. 12805, para 1), reading on a subvolume of said sample; analyzing the fluctuations of said fluorescence, (Walter et al. at p. 12805, para 1); and determining the presence or absence of said pathogen component.

Walter et al., throughout the publication, abstract, and at para 1, teach measuring pathogen genomic sequences, particularly of Mycobacterium tuberculosis, and teach a fluorescence correlation spectroscopy method employing fluctuation autocorrelation (p. 12805) for assaying the pathogen.

The examiner respectfully submits that Weiner teaches fluorescence correlation spectroscopy (FCS) comprising measuring fluorescence from a volume element, reading on measuring the fluorescence from a subvolume of said sample, (see p. 85, second paragraph and last paragraph).

Walter et al., e.g., in the abstract, teach analysis for 30 seconds. Walter, at p. 12810, para 2, teaches multiplex analysis with different labeled probes, which read on a plurality of unique fluorescently-tagged probes.

(10) Claim Rejections - 35 USC § 103

16. Claims 59-66 and 118-125, 127, 128, 130-138 are rejected under 35 U.S.C. 103(a) as being unpatentable by **Kask**, US 6,515,289, in view of **Lahiri et al.**, US 2003/0138853 A1.

Response to Arguments In The Brief

Appellant argues that the rejection should be reversed because there is no reason, teaching, suggestion or motivation to combine the teachings of Kask and Lahiri et al., (Brief at p. 41).

In regard to the rejection of claim 59, appellant argues that although Kask discloses units of samples that can be bacteria or viruses, Kask does not teach or suggest characterizing a virus or bacterium with any specific physical property. Appellant argues that it is undisputed that Kask fails to teach a sample that includes a pathogen. Brief at p. 41. In particular, appellant argues that Kask does not teach characterizing a virus or bacterium by analyzing the fluctuations in fluorescence due to the diffusion or flow of a bacterium or virus through a subvolume.

Appellant argues that Kask is interested in interactions with receptors on the cell or vesicle and that none of the examples of Kask involve analyzing bacteria or viruses in general, or analyzing the diffusion or flow of a bacterium or virus in particular.

Appellant argues that the fact that some of the claims of Kask mention that a sample includes a bacteria or a virus, that fact is "of no moment." Also, the fact that some claims of Kask mention "fluctuations" "is irrelevant". Brief at p. 43. Kask does not provide the skilled artisan with reason to analyze fluctuations in fluorescence due to the diffusion or flow of a pathogen through a subvolume.

Appellant argues that Lahiri et al. do not cure the deficiencies of Kask. Appellant argues that Lahiri et al. do not teach a sample that includes a

pathogen. Appellant argues that because Lahiri et al. teach that their arrays can used to detect analytes that are indicative of disease and that these analytes are not inherently, i.e., necessarily, pathogens. Rather these analytes are indicators of pathogens, and not pathogens themselves, as the claims require. Thus Lahiri et al. do not teach that actual pathogens are being analyzed or that actual pathogens are in the sample. Therefore, the claim element of samples that include pathogens is not taught by Lahiri et al.

Appellant argues that the fact that Lahiri et al. disclose that their biological membrane array can be interfaced with a number of detection methods, including fluorescence correlation spectroscopy, is "of no moment". Appellant argues that "[n]othing in such a disclosure specifically directs the skilled artisan to employ fluorescence correlation spectroscopy in combination with a pathogen –let alone to analyze the fluctuations in fluorescence due to diffusion or flow of a pathogen through a subvolume of a sample", (Brief at p. 44). Appellant argues that because "Lahiri et al. seek to immobilize a pathogen on their array, (Brief at p. 44), the "skilled artisan would refrain from event attempting to analyze the fluctuations in fluorescence due to diffusion or flow of a pathogen through a subvolume of a sample, because the pathogen of Lahiri et al. would not be diffusing or flowing."

In regard to claim 62, appellant argues that Kask does not teach or suggest a samples that includes a pathogen, let alone a plurality of unique fluorescently tagged probes capable of binding a unique pathogen. Appellant argues "[t]o the contrary, Kask discloses that the dyes all bind to the same target,

(Kask, col. 8, lines 18-29)." Brief at p. 45. Appellant argues that the reference of Lahiri et al. does not cure the deficiencies of Kask.

In regard to claim 120, appellant argues that neither Kask nor Lahiri et al. teach or suggest a probe that includes multiple binding sites for a pathogen.

In regard to claim 121, appellant argues that neither Kask nor Lahiri et al. teach or suggest a pathogen that includes multiple binding sites for binding a probe.

In regard to claim 126, appellant argues that claim 126 is rejected over Kask and in view of Lahiri et al. However, as stated in the Advisory Action, the examiner respectfully submits that claim 126 is not so rejected.

In regard to claim 127, appellant argues that neither Kask nor Lahiri et al. teach or suggest obtaining a measured correlation function of a pathogen and applying a correction algorithm to the measured correlation function.

In regard to claim 132-137, appellant argues that neither Kask nor Lahiri et al. teach or suggest teach analyzing the fluctuations in fluorescence due to diffusion or flow of a pathogen through a subvolume of a sample over a period of seconds.

In regard to claim 138, appellant argues that neither Kask nor Lahiri et al. teach or suggest a sample that includes a plurality of unique fluorescently tagged probes each of which is capable of binding to a unique pathogen, as in claim 138.

Appellant's arguments have been fully considered but the examiner respectfully submits that these arguments are not persuasive.

In regard to the nature of the claimed invention, the examiner respectfully notes that the first sentence of the Detailed Description section of the instant Specification states:

> **The present invention provides a method of screening** members of a library (e.g., proteins produced from a cDNA library) **using fluorescence correlation spectroscopy**. The method includes screening a sample that includes a sub-volume of the library, at least one probe and at least one fluorescent tag to determine whether a probe binds to a member of the library under equilibrium conditions.

Specification at p. 17, lines 23-27, (emphasis added). Thus the present invention of the application uses the method of fluorescence correlation spectroscopy (FCS).

The examiner respectfully notes that the instant Specification teaches:

> **Fluorescence correlation spectroscopy (FCS) is a single molecule detection method that measures the fluctuations in fluorescence intensity in a small (e.g., femtoliter) confocal volume.** FCS employs a tightly focused laser beam to define the confocal volume. The diffusion of fluorescently labeled particles into and out of the illuminated volume determines the fluorescence intensity fluctuation patterns. From this data, one can extract both qualitative information and quantitative information on the molecule being studied. Such qualitative information includes, e.g., the presence or absence of molecular interaction; such quantitative information includes diffusion time, stoichiometry of the interactions, concentration of the interacting particles and the kinetics of the interaction.

Specification at pp. 1-2, bridging paragraph, (emphasis added). Thus fluorescence correlation spectroscopy is a long established procedure that measures fluctuations in fluorescence intensity.

The examiner respectfully notes that in subsection III.A. the Specification states:

> A. PROBES FOR PATHOGEN DETECTION
>
> **Various probes can be prepared for use in detecting pathogens. Antigens of the pathogens, for example, can be detected using specific antibody probes and nucleic acid sequences of the pathogen can be detected using specific oligonucleotide probes.** The probes preferably are selected to target glycoproteins, proteins, nucleic acids, or combinations thereof, which may include specific portions of the pathogen, a spore of the pathogen, toxins, metabolic products of the pathogen, biological responses induced by the pathogen. The specific probe-sets can be prepared based on genomic data, the characterization of the expressed proteome, and clinical data on outcomes of infection.
>
> Oligonucleotide probes can be designed based on information obtained using Polymerase Chain Reaction, PCR, and the analysis of genomic data for variable and conserved regions of DNA in related pathogen species. Antibody probes can be designed for unique antigens expressed by specific pathogens as determined by genomic and proteomic database analysis. **Pathogenic virulence can often be traced to unique expression of one or more proteins or glycoproteins. Such unique expression of one or more proteins or glycoproteins can serve as a specific probe target.**

Specification at p. 30, lines 15-30. Thus the Specification contemplates the detection of pathogens using antibody or oligonucleotide probes, which detect, for example, antigens or nucleic acid sequences, respectively, of the pathogens.

The examiner respectfully notes that the Specification states:

> IV. THE TARGET
>
> The target can include any target of interest. The target can be unknown or known. Unknown targets include those targets to which it is not known whether or not the probe binds. Known targets include those targets to which a binding site of a probe of interest binds. **Examples of suitable targets include macromolecules**

> **(e.g., proteins, peptides, polynucleic acids, and polysaccharides), molecules (e.g., amino acids, nucleic acids, and saccharides), and combinations thereof. Useful macromolecules include, e.g., antibodies, receptor proteins, lectins, hormones, protein A, protein G, avidin, enzymes, and combinations thereof.**
>
> The target can be a library, a portion of a library, a member of a library or a combination thereof. Suitable libraries include, e.g., apatamer libraries, phage display libraries, antibody libraries, peptide libraries, and translated cDNA libraries. Examples of members of a library include proteins, peptides, polynucleic acids, organic polymers, polysaccharides, amino acids, nucleic acids, and saccharides.

Specification at p. 31, line 26-p. 32, line 8, (emphasis added). Thus the Specification teaches that the target can include those targets to which a binding site of a probe of interest binds; and that targets of the instant invention include proteins, peptides, nucleic acids, etc.

Appellant's arguments have been considered but are not persuasive. Firstly, as stated in the previous Office action, claims must be given their broadest reasonable interpretation consistent with the supporting description. In re Hyatt, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). The claims are drawn to assaying for a pathogen in a sample. See, *e.g.*, *Invitrogen Corp v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 1997); and MPEP 211.03.

For the purpose of construing claims, the Specification states:

> Other suitable targets include **organisms including e.g., pathogens (e.g., bacterial, viral, rickettsia), pathogen components**, toxins, and macromolecules associated with an organism. Examples of **pathogen components include pathogens, pathogen fragments, pathogen nucleic acids, pathogen proteins**, pathogen carbohydrates, pathogen spores,

> pathogen toxins, metabolic products of pathogens, and combinations thereof.

Specification at p. 33, lines 5-9, (emphasis added). The examiner respectfully submits that this passage is not straightforward. The initial sentence of this passage states that "targets" include "organisms" that include, for example, pathogens, such as bacteria, viruses and rickettsia. However this sentence also states that organisms include "pathogen components", "toxins" and "macromolecules associated with an organism". The aforementioned passage further provides examples of the said "pathogen components", that include pathogens, pathogen proteins and pathogen nucleic acids. Thus the Specification teach organisms as including pathogen components that are pathogen protein and pathogen nucleic acids, for example. Therefore, the examiner respectfully submits that appellant's reading of the term "pathogen" as necessarily drawn to "organisms" can be taken to mean that the term "pathogen" includes pathogen fragments, pathogen nucleic acids, pathogen proteins, et cetera.

The examiner further respectfully submits that appellant's arguments place too restrictive an interpretation of the claim term "pathogen". The Specification does not appear to provide a limiting definition of the term pathogen, which provides bacteria and viruses as *examples* of pathogens, including the specific example of the bacterial genus rickettsia. The examiner respectfully submits that the claim term "pathogen", given its broadest interpretation consistent with the Specification, can include pathogen

components, pathogen fragments, pathogen nucleic acids, pathogen proteins, pathogen carbohydrates, pathogen spores, pathogen toxins, metabolic products of pathogens, and combinations thereof.

Secondly, the examiner respectfully submits that one of ordinary skill in the art would understand the term pathogen as to not be restricted to microorganisms. As stated in the previous Office actions, Dorlands's Illustrated Medical Dictionary, Twenty-fifth Edition, Saunders, Philadelphia (1979, of record), at p. 1148, defines the term pathogen as "any disease-producing microorganism **or material**", (emphasis added).

Furthermore, the instant Specification, e.g., at p. 31, lines 6-7, teaches that "[t]he probes can be designed to detect the pathogen, toxins secreted by the pathogen and combinations thereof." The instant Specification at p. 31, lines 14-15, states that "[p]robes can be designed to specifically bind target DNA sequences and target viral coat proteins". Thus, the examiner respectfully submits that the instant Specification contemplates toxins and viral DNA as examples of disease-producing materials that are pathogens.

The examiner respectfully notes that the reference of Kask states:

> New opportunities for assay development were opened when the technology for monitoring fluorescence from single fluorophore molecules became available. The first successful studies on fluorescence intensity fluctuations were performed by Magde, Elson and Webb (Biopolymers, Vol. 13, 29-61, 1974) who demonstrated the possibility to detect number fluctuations of fluorescent molecules and established a research field called fluorescence correlation spectroscopy (FCS). FCS was primarily developed as a method for determining chemical kinetic constants and diffusion coefficients. The experiment consists essentially in measuring the variation of the number of molecules of specific reactants in time in

> a defined open volume of solution. Microscopic fluctuations of the concentration of the reactant are detected as fluorescence intensity fluctuations from a small, open measurement volume. The measurement volume is defined by a focussed laser beam, which excites the fluorescence, and a pinhole in the image plane of the microscope collecting fluorescence. Intensity of fluorescence emission fluctuates in proportion with the changes in the number of fluorescent molecules as they diffuse into and out of the measurement volume and as they are created or eliminated by the chemical reactions. Technically, the direct outcome of an FCS experiment is the calculated autocorrelation function of the measured fluorescence intensity.

Kask at col. 1, lines 22-47.

Thus Kask teaches that fluorescence correlation spectroscopy (FCS) was developed to measure the variation of the number of molecules of specific reactants in time in a defined open volume of solution. Kask teaches that microscopic fluctuations of the concentration of the reactant are detected as fluorescence intensity fluctuations from a small, open measurement volume. Thus Kask teaches that methods measuring fluorescence fluctuation were well-known in the art.

As appellant notes, Kask teaches units of a sample that include fluorescently labeled or naturally fluorescent molecules, molecular complexes, vesicles, cells, beads and other particles in water or other liquids may be examples of fluorescent units in liquid samples, while examples of fluorescent units of a solid sample are impurity molecules, atoms or ions, or other fluorescence centers, (Kask at col. 3, lines 40-52). Again, Kask state:

> According to a further preferred embodiment, the units are particles, molecules, aggregates, vesicles, cells, viruses, bacteria, centers, or mixtures thereof in solids, liquids or gases. It might be preferred to group units into species which can be distinguished by

> at least one of their specific physical properties. At least one of the species can be luminescent, preferably fluorescent, and/or can be luminescently labeled.

Kask at col. 6, lines 31-37. Thus Kask contemplates appropriate targets as including particles, molecules, aggregates, vesicles, cells, viruses, and bacteria.

The examiner respectfully submits that one of ordinary skill in the art would have been motivated at the time of the invention to have used methods of detecting molecules, bacteria and viruses using fluorescence correlation spectroscopy, as taught by Kask, to detect pathogens, as taught by Lahiri et al.

Lahiri et al. teach an array that may be used to assay for pathogens. Lahiri et al. state:

> [0077] The array may be used in a diagnostic manner when the plurality of analytes being assayed are indicative of a disease condition or the presence of a pathogen in an organism. In such embodiments, the sample which is delivered to the array will then typically be derived from a body fluid or a cellular extract from the organism.

Lahiri et al. at para [0077]. The examiner respectfully submits that Lahiri et al. would have suggested to one of ordinary skill in the art to assay for pathogens.

The examiner further submits that Lahiri et al. would have suggested to one of ordinary skill in the art to assay for pathogens by fluorescence correlation spectroscopy and as taught by Kask. Lahiri et al. state:

> [0071] A wide range of detection methods is applicable to the methods of the invention. As desired, detection may be either quantitative, semiquantitative, or qualitative. The invention array can be interfaced with optical detection methods such as absorption in the visible or infrared range, chemoluminescence, and fluorescence (including lifetime, polarization, **fluorescence correlation spectroscopy (FCS)**, and fluorescence-resonance energy transfer (FRET)). Furthermore, other modes of detection

> such as those based on optical waveguides (PCT Publication WO96/26432 and U.S. Pat. No. 5,677,196), surface plasmon resonance, surface charge sensors, and surface force sensors are compatible with many embodiments of the invention.

Lahiri et al. at para [0071].

Appellant argues that the target of Lahiri et al. would be incapable of diffusing. The examiner respectfully submits that this is not persuasive. Firstly, the reference of Kask teaches using fluorescence correlation spectroscopy (FCS) to detect molecules, bacteria and viruses by analyzing fluctuation of fluorescence.

Secondly, Lahiri et al. states:

> [0072] The assays used on these arrays may be **direct, non-competitive assays or indirect, competitive assays. In the noncompetitive method**, the affinity for binding sites on the probe is determined directly. In this method, the proteins in the microspots are directly exposed to the analyte ("the target"). The analyte may be labeled or unlabeled. **If the analyte is labeled, the methods of detection would include fluorescence**, luminescence, radioactivity, etc. If the analyte is unlabeled, the detection of binding would be based on a change in some physical property at the probe surface. This physical property could be refractive index, or electrical impedance. The detection of binding of unlabeled targets could also be carried out by mass spectroscopy. **In the competitive method, binding-site occupancy is determined indirectly.** In this method, the proteins of the array are exposed to a solution containing a cognate labeled ligand for the probe array and an unlabled target. **The labeled cognate ligand and the unlabled target compete for the binding sites on the probe protein microspots.** The affinity of the target for the probe microspot relative to the cognate ligand is determined by the decrease in the amount of binding of the cognate labeled ligand. The detection of binding of the target can **also be carried out using sandwich assays** in which after the initial binding, the array is incubated with a second solution containing molecules such as labeled antibodies that have an affinity for the bound target, and the amount of binding of the target is determined based on the amount of binding of the labeled antibodies to the probe-target complex.

Lahiri et al. at para [0072]. Lahiri et al. thus contemplates different variations of using their arrays. These variations include indirect, competitive assays, wherein unlabeled target diffuses and flows on the array to compete with a labeled cognate ligand, which has a specificity that is similar to the target, in order to prevent binding of the labeled cognate and thereby affect the fluorescence fluctuation of the label. Appellant's argument that any target detected by Lahiri et al. is immobilized on the array of Lahiri et al. and therefore the target is incapable of diffusing does not consider these indirect, competitive assays of the method of Lahiri et al.

Furthermore, the examiner respectfully submits that analysis of fluorescence fluctuation would include measuring the absence of fluorescence fluctuation. The examiner submits that the absence of fluctuation would result in a dwell time of long duration.

Therefore, the examiner respectfully submits that appellant's assertion FCS cannot be employed in the arrays of Lahiri et al., even though Lahiri et al. teach using FCS, is not based upon objective evidence and is merely the arguments of counsel.

In regard to claims 62 and 138, appellant argues that Kask does not teach or suggest a samples that includes a pathogen, let alone a plurality of unique fluorescently tagged probes capable of binding a unique pathogen. Appellant argues "[t]o the contrary, Kask discloses that the dyes all bind to the same target,

(Kask, col. 8, lines 18-29)." Brief at p. 45. Appellant argues that Lahiri et al. do not cure the deficiencies of Kask.

At Example 2, Kask teaches the detection of dyes with different specific physical properties, wherein the physical properties relate to numbers of events as detected by two optical filters detecting different nm light, (Kask at col. 12, lines 25-55). These dyes are tetramethylrhodamine (TMR) and Rhodamine Red X (RRX). Kask, at Example 2 and Figures 6c and 7c, show resolution of a sample mixture of TMR and RRX solutions into two distinguishable peaks using fluorescence correlation spectroscopy. Kask teaches their method as particularly well suited to diagnostic purposes, for particle sorting, nucleic acid sequencing, "or for general analytical purposes, such as environmental analytics or process control", (Kask at col. 7, lines 36-42). Kask teaches the screening use of a luminescently labeled ligand to cell receptors, (Kask at col. 7, lines 43-50). Kask at col. 7, line 65-col. 30, teach labeled probe molecules. The respectfully examiner submits that it would have been obvious to one of ordinary skill in the art to assay a plurality of unique fluorescently tagged probes capable of binding a unique pathogen

Furthermore, Lahiri et al. teach arrays of different proteins that are probes. Lahiri et al. state:

> [0075] Another embodiment of the invention provides a method of assaying in parallel for the presence of a plurality of analytes in a sample which can react with one or more of the proteins on the array. This method comprises delivering the sample to the array and detecting for the interaction of the analyte with the protein at each microspot.

Lahiri et al. at para [0075].

In regard to claim 120, appellant argues that neither Kask nor Lahiri et al. teach or suggest a probe that includes multiple binding sites for a pathogen.

Lahiri et al., at para [0072], teach the use of labeled antibodies that have affinity for bound target, which describes probes for multiple binding sites, and wherein the target is a pathogen, as explained above.

In regard to claim 121, appellant argues that neither Kask nor Lahiri et al. teach or suggest a pathogen that includes multiple binding sites for binding a probe.

Kask, at col. 8, lines 18-29, teaches diagnostic methods to identify target nucleic acid strands, which contain different antisense binding sites to different probes that are different, short primers.

In regard to claim 126, appellant argues that claim 126 is rejected over Kask and in view of Lahiri et al. The examiner respectfully submits that claim 126 is not so rejected.

In regard to claim 127, appellant argues that neither Kask nor Lahiri et al. teach or suggest obtaining a measured correlation function of a pathogen and applying a correction algorithm to the measured correlation function.

Kask, at col. 13, lines 54-58, teach brightness corrected fluorescence correlation spectroscopy data, which reads on obtaining a measured correlation function of a pathogen and applying a correction algorithm to the measured correlation function.

In regard to claim 132-137, appellant argues that neither Kask nor Lahiri et al. teach or suggest teach analyzing the fluctuations in fluorescence due to diffusion or flow of a pathogen through a subvolume of a sample over a period of seconds.

Kask at col. 12, lines 6-9, teaches five fluorescence correlation spectroscopy experiments wherein each experiment was 40 seconds, which describe *analyzing* fluctuations in fluorescence over a period of seconds.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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PRIMARY EXAMINER

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